

## **REMARKS**

### **Claim amendments**

Claim 25 is amended herein to correct minor typographical errors. No new matter has been added.

### **Rejection of Claim 25 Under 35 U.S.C. 103(a)**

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al., WO00/06588. Krieg is alleged to suggest introducing a 3'-3' linkage into an immunostimulatory oligonucleotide.

Applicants respectfully disagree. Claim 25 recites a method for modulating an immune stimulatory oligonucleotide by introducing specific modifications into the oligonucleotide. These modifications are limited to a 3'-3' linkage, 1',2'-dideoxyribose, C3-linker, Spacer 9, Spacer 18, 2-aminobutyl-1,3-propanediol linker,  $\beta$ -L-deoxynucleoside, amino linker, 2'-O-propargyl-ribonucleoside, 3'-deoxynucleoside, or a 2'-5' linkage. Krieg neither teaches nor suggests any of these specific modifications.

The presently maintained rejection focuses on the 3'-3' linkage and cites Krieg as suggesting at page 13 "the substitution of the natural phosphodiester backbone that links nucleosides with a 3'-3' linkage to stabilize the oligonucleotides." Applicants quote the selected passage from Krieg to demonstrate that Krieg does not even mention introducing a 3'-3' linkage into an immune stimulatory oligonucleotide and thus does not make any such suggestion. Krieg states, in relevant part:

Alternatively, nucleic acid stabilization can be accomplished via phosphate backbone modifications. Preferred stabilized oligonucleotides of the instant invention have a modified backbone. It has been demonstrated that modification of the oligonucleotide backbone provides enhanced activity of the CpG oligonucleotides when administered *in vivo*. These stabilized structures are preferred because the chiral CpG molecules of the invention have at least a partial modified backbone. CpG constructs, including at least two phosphorothioate linkages at the 5' end of the oligonucleotide and multiple phosphorothioate linkages at the 3' end, preferably 5, provide maximal activity and protect the oligonucleotide from degradation by intracellular exo- and endo-nucleases. Other modified oligonucleotides include phosphodiester modified oligonucleotides, combinations of phosphodiester and phosphorothioate oligonucleotide, methylphosphonate, methylphosphorothioate, phosphorodithioate, and combinations thereof.

Where is the suggestion to introduce a 3'-3' linkage into an immune stimulatory oligonucleotide, or any of the other specific modifications recited in claim 25, for that matter? It simply isn't there. To render a claim obvious a cited prior art reference must provide such a teaching that would make one of ordinary skill in the art immediately envision the claimed invention. Clearly, Krieg, quoted above, does not meet this standard.

The rejection goes on to state that "One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the use of 3'-3' linkage to stabilize oligonucleotides is routinely practiced in the art." However, no reference is provided to substantiate this latter assertion. It is important to note that the only prior art relied upon in this rejection is Krieg, which as demonstrated above, does not suggest any of Applicants specified modifications, including a 3'-3' linkage.

This rejection is thus improper, especially in a final office action, because it shifts the burden of proof to the Applicant to demonstrate that no such unspecified prior art exists anywhere in the universe that suggests that any of the claimed modifications can be used in an immune stimulatory oligonucleotide to stabilize the oligonucleotide without destroying the immune stimulatory activity of the oligonucleotide. Applicants are unaware of any such prior art, but it is not Applicants' burden to show that such unspecified prior art does not exist. The burden is on the PTO to specify what references it is relying upon for this proposition, which it did not do in this rejection. Applicants cannot rebut an alleged teaching from the prior art when no particular prior art is specified, since there is no specific prior art for Applicants to analyze and argue against.

Thus, Applicants respectfully request that the PTO provide specific prior art to support its rejection and remove the finality of the rejection, or, preferably, simply withdraw the rejection.

### **CONCLUSION**

In view of the above amendments and remarks, it is believed claim 25 is in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner believes that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned attorney at 781-933-6630.

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Respectfully submitted,

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